REMARKS

Claims 34, 42, 45, 46, and 47 are pending in this application. Claims 1-33, 35-41, 43 and 44 have been cancelled. Claim 34 has been amended. The basis for new claim 47 is found in claims 34 and 42 and the claim contains no new matter.

I. Examiner's Position

The Examiner has rejected Claims 34, 42, 45, and 46 under 35 U.S.C. 103(a) as being unpatentable over Nadkarni (WO 03/104192) in view of Staniforth (U.S. 5,004,614). It is the Examiner's position that Nadkarni et al. teaches controlled release formulations of lamotrigine. According to the Examiner, Nadkarni et al.'s formulation is a core comprising lamotrigine, a release retarding polymer such as HPMC, compression aid/diluent such as microcrystalline cellulose, binder such as povidone, and further teaches that glidants such as magnesium stearate, talc, etc. can be added, and core particles can be coated with a polymer such as a rate controlling polymer such as poly(methyl methacrylate), poly(ethyl methacrylate) in 5 to 60% of core particles.

The Examiner points out that Nadkarni does not teach the thickness of the outer coating nor an outer coating with one or more orifices. For this teaching the Examiner uses the Staniforth reference. The Examiner states that Staniforth teaches the use of one or more orifices and coatings, that release-modifying agents may be used to slow the release of active agent from the device, and provides examples of such agents include soluble polymers. The Examiner asserts that Staniforth teaches that the thickness of the coating necessary to provide results may be simply determined by one of ordinary skill in the art via the preparation of devices with differing coating thicknesses, performing dissolution tests in the devices without the inclusion of an orifice in the device, and choosing the coating thickness which does not allow the release of the active agent (drug) from the device during the desired duration of controlled release.

From all of the above, the Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Nadkarni and Staniforth to make a sustained release formulation

of lamotrigine with an outer coat covering said core impermeable to environmental fluids even though Nadkarni and Staniforth employ different techniques for controlled release.

The Examiner also notes that neither of the references explicitly teaches the outer coat dissolves when the surrounding pH exceeds 5, but points out that one of ordinary skill would be motivated to use the appropriate pH that would simulate *in vivo* conditions to get an idea of how the composition would behave in the human body. The Examiner concludes that it is within the level of ordinary skill in the art to manipulate the formulation and pH parameters to achieve the desired release profile over a range of pH environments.

The Examiner points out that the reference does not teach the AUC values or the Cmax values after administration of sustained release formulation of lamotrigine as in Claim 42. It is the Examiner's assertion that it would have been obvious to one of ordinary skill in the art that the sustained formulation comprising lamotrigine having a Cmax less than the instant release tablet containing the same amount of lamotrigine because Nadkarni teaches that the controlled release lamotrigine is designed to avoid excessive Cmax levels and will produce lower plasma concentration, which are reached over a longer period of time. Also, according to the Examiner it is obvious to one of ordinary skill in the art that the sustained release formulation comprising the same composition taught by the teachings of Nadkarni and Staniforth will have the same release profile and properties such as AUC and Cmax values.

II. Applicants' Argument

It is Applicants' position that the formulations embodied in Claims 34, 42, 45, 46, and 47 are not obvious under 35 USC 103(a) as being unpatentable over Nadkarni (WO 03/104192) in view of Staniforth (U.S. 5,004,614).

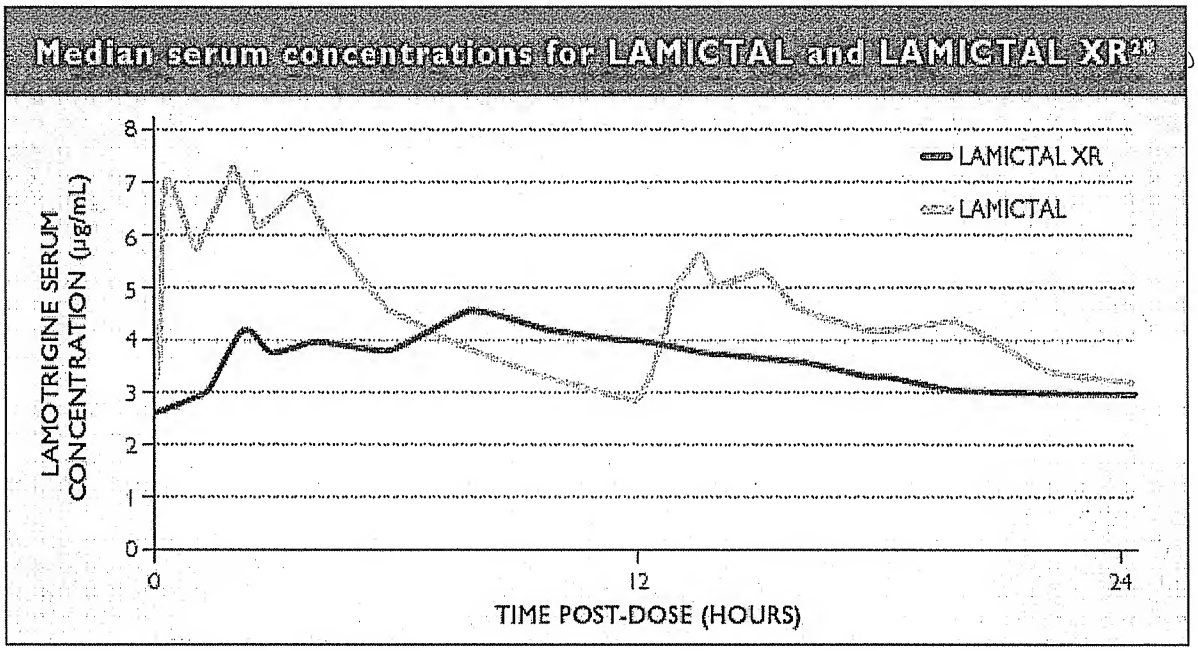
The Invention

Existing marketed tablet formulations of lamotrigine provide immediate release of the active ingredients once the tablet reaches the stomach. The peak plasma concentrations occur anywhere from 1.4 to 4.8 hours following drug administration. The disadvantage is that the plasma concentration (pharmacokinetic profile (PK)) achieved with conventional tablets is cyclical, with peaks occurring after administration followed by troughs occurring before the next administration of drug.

In particular for the treatment of epilepsy it is thought that the troughs may lead to breakthrough seizures and the peak plasma concentration may result in some adverse events (AE) occurring in some patients or alternatively the rate of increase in plasma concentration in the initial stages before the peak plasma concentration is achieved may also affect the AE profile.

The currently claimed invention is a sustained release formulation of lamotrigine which has two phases in the release of lamotrigine, wherein the release rate in the first phase (in the stomach) is slower than the release rate in the second phase (once the pH is above 5, i.e. in the small intestine).

When the steady state pharmacokinetics of the currently claimed invention given once a day (Lamictal XR™) is compared to lamotrigine immediate release (Lamictal™) given twice a day it is clear that the median trough and peak plasma levels of the sustained release formulation given once a day lie within those of the twice daily immediate release formulation and has less plasma level fluctuation than the twice daily immediate release formulation (see diagram below).



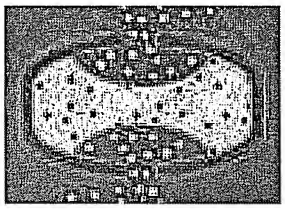
Based on these data the FDA has approved Lamictal XR™ as a once daily dose of lamotrigine and the product was launched in July 2009.

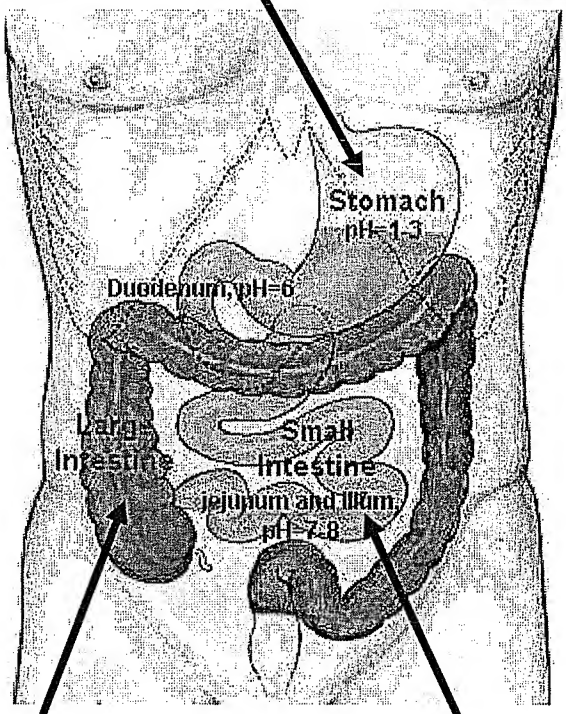
The reduction in peaks and troughs in the serum concentration of lamotrigine from Lamictal XR™ is achieved by tightly controlling how fast and where the lamotrigine is released from the sustained release formulation.

Orifices in the enteric coating of Lamictal XR™ control how much of the core is exposed in the stomach (slowing the rate of lamotrigine release from the core) and release retarding polymer(s) present within the core further slows the release rate of lamotrigine. The first phase of lamotrigine release is therefore slow. Once the tablet reaches the higher pH environment of the small intestine, the enteric coat dissolves. This exposes the entire surface area of the core, allowing both erosion and diffusion of lamotrigine from the core, which increases the speed of release. The second phase of release is therefore faster than the first.

The two phases of lamotrigine release from the formulation of the invention are depicted in the following diagrams.

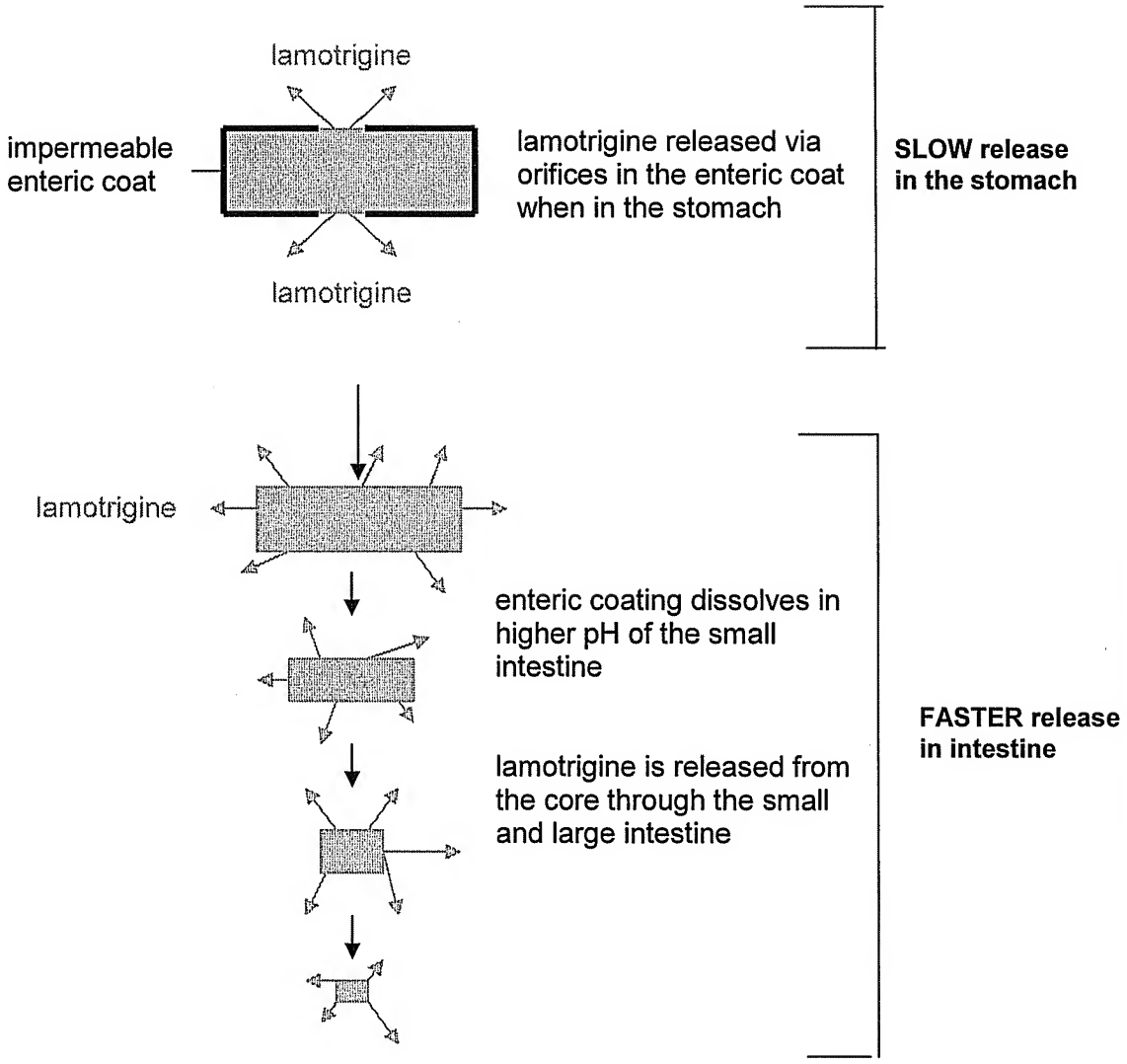
1. Tablet in stomach
Controlled release of lamotrigine through orifices in an enteric coating which limits the level of core exposed under the acidic conditions of the stomach.





2. Tablet in small intestine
Enteric coat dissolves, fully exposing the core, allowing erosion and diffusion of lamotrigine through the small intestine.

3. Tablet in large intestine
Absorption of lamotrigine continues as remainder of tablet travels through the intestine.



Retarding release in the stomach using the currently claimed formulation also overcomes the pH dependency of lamotrigine solubility in the gastro-intestinal tract (it's approximately 20-30 times more soluble in the acidic environment of the stomach than in the small and large intestine). This produces a slower rate of absorption into the bloodstream than that of immediate release lamotrigine tablets to reduce the peak and trough plasma concentrations of immediate release lamotrigine (as shown in the first graph) creating the potential for improved seizure control and reduction of adverse side effects in patients with epilepsy.

Claim 34 of the current application recites,

> "A sustained release formulation of lamotrigine or a pharmaceutically acceptable derivative thereof in which there are two phases in the release of lamotrigine or a pharmaceutically acceptable derivative thereof, wherein the release rate in the first phase takes place in the oesophagus and stomach and is slower than the release rate in the second phase which takes place when the surrounding pH exceeds 5...".

The description of the current specification further expands on the need for a slow first phase of release in the stomach and a faster second phase of release in the intestine, discussing how much less lamotrigine needs to be released in the first phase compared to the faster second phase (paragraphs [0121] to [0124] of Applicants' published specification).

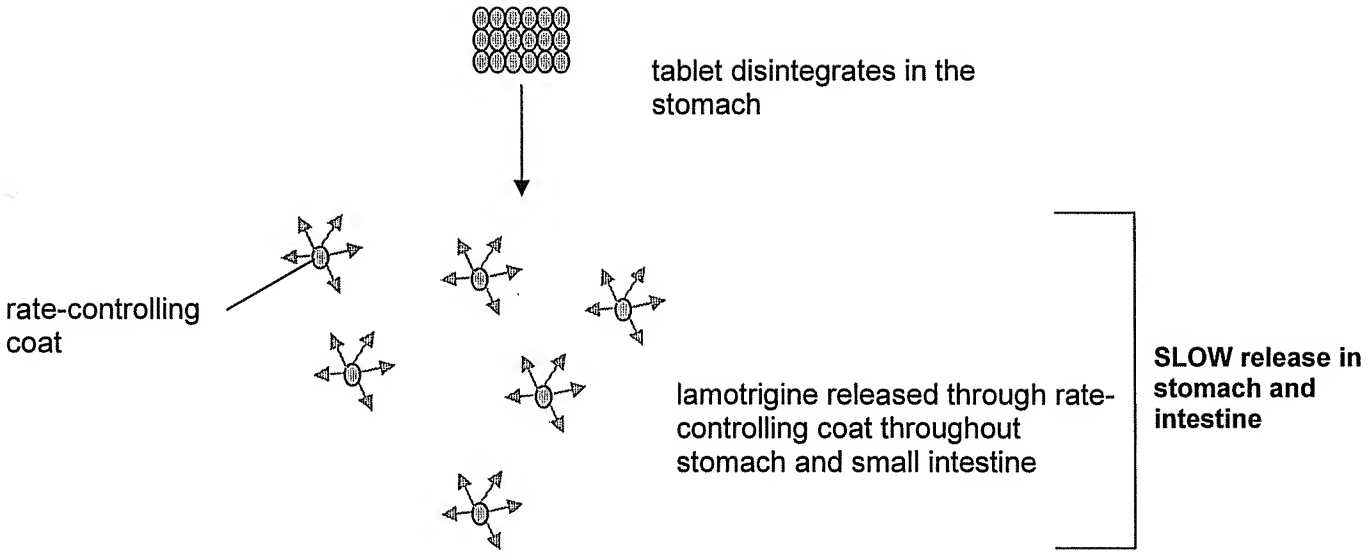
Non-obviousness Argument. The Examiner has rejected the current claims as being unpatentable over Nadkarni (WO 03/104192) in view of Staniforth (U.S. 5,004,614). The Applicant thinks that this is based on a misunderstanding of the disclosures set out in Nadkarni and Staniforth and that once the prior art formulations have been explained in detail the Examiner will accept that there is no motivation to combine the two references and that even if they were to be artificially combined the result would not be the currently claimed invention.

Nadkarni

Nadkarni discloses rapidly disintegrating multiparticulate formulations of immediate release lamotrigine coated by polymers which provide controlled release profiles of the immediate release lamotrogine, whether the particles are contained in tablets or capsules.

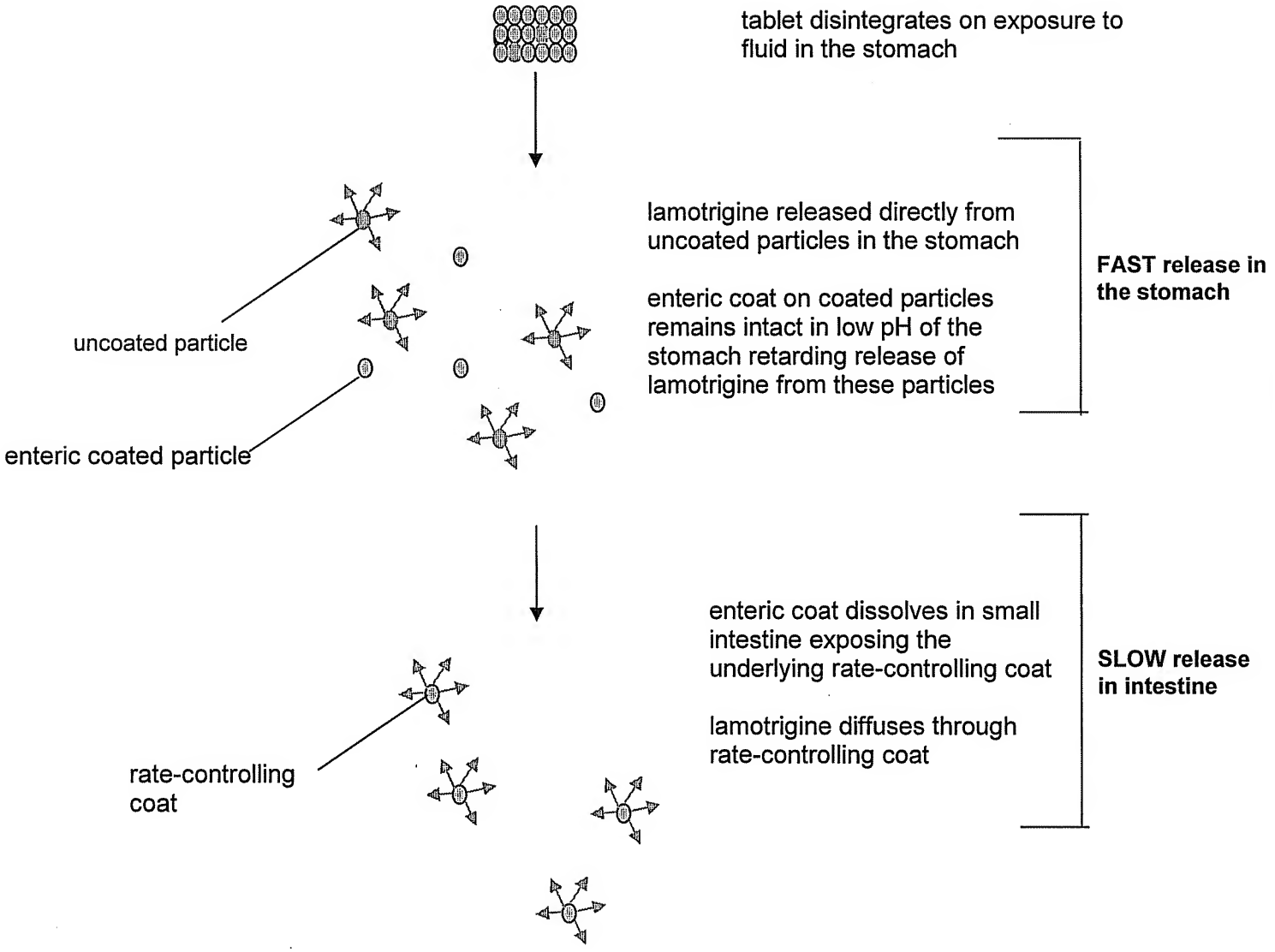
Eleven of the twelve examples given in the application relate to rate-controlling coatings that retard the release of lamotrigine from the particles (slow release).

Examples 1 to 11:



The remaining example in Nadkarni (Example 12) is a mixture of uncoated particles of lamotrigine and particles of lamotrigine coated with two coats, the first a rate-controlling coat and the second, outer coat is enteric (dissolves at pH 5 or above).

Example 12 :



As in Examples 1 to 11, the tablet of Example 12 disintegrates in the stomach, exposing the particles. Lamotrigine is immediately released from the uncoated particles (the first phase of release is therefore fast). This lamotrigine would pass through the stomach and be immediately absorbed through the small intestine providing an initial burst of lamotrigine in the blood.

Meanwhile, the enteric coated particles remain intact until they pass out of the stomach (a low pH environment). When they enter the small intestine (a high

pH environment, pH 5 or above) the outer enteric coat dissolves to expose the rate-controlling coating.

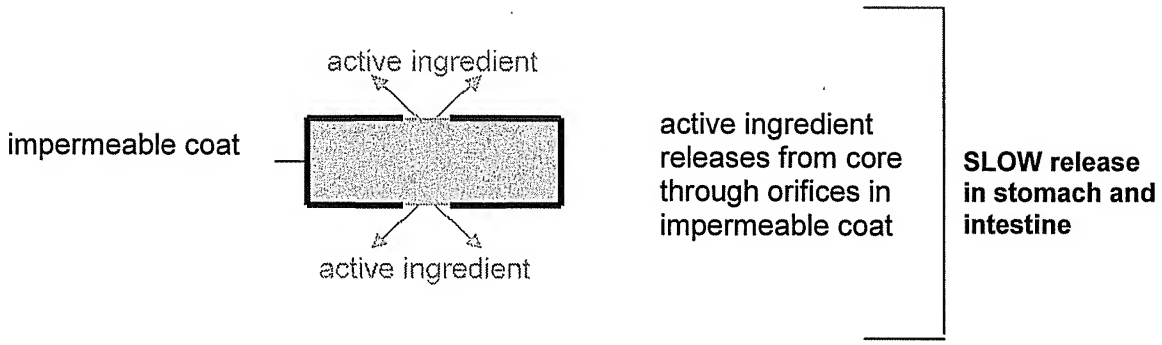
The lamotrigine is then released from the particles through the rate-controlling coating (made more permeable as the enteric part of the permeable coating (Eudragit L 30D polymer) also dissolves in this environment). The release of the lamotrigine from the particles is therefore controlled at the surface of the particles via the rate-controlling coat. The Nadkarni second phase of release is therefore slower than that of the first phase.

The core formulation of lamotrigine in all of the Nadkarni Examples contains a binder. This is either HPMC E-15 LV (Examples 1-10) or HPMC 6cps (Examples 11 and12). Both HPMC E-15 LV and HPMC 6cps are polymers with low viscosity and are acting as binders. Polymers with high viscosities, measured in thousands of centipoise (cP) act as release retarding polymers (p. 252, 1st paragraph left column, Kibbe et al (2000) "Handbook of Pharmaceutical Excipients". Pharmaceutical Press, London, copy attached).

The only two phase delivery taught by Nadkarni is fast and then slow release. The currently claimed invention of Applicants has a slow first phase and a faster second phase of lamotrigine release.

Staniforth

Staniforth discloses formulations with an impermeable coating with orifices in the coating. The core is exposed to the external environment via the orifices in the coating through which the unspecified active ingredient is released. The release of the unspecified active ingredient is also dependent on the solubility profile of the active ingredient itself, the external environment and the composition of the core.



Staniforth does not disclose formulations with two phases of release, nor is it specifically directed towards formulations comprising lamotrigine.

No motivation to combine the teachings of Nadkarni and Staniforth

Nadkarni relates to tablets that are designed to disintegrate in the stomach. Staniforth relates to tablets that are designed to avoid disintegration in any part of the gastro-intestinal tract. Therefore, the person skilled in the art would not even consider combining these two different approaches.

Summary

The Examiner is using hindsight to piece together the currently claimed invention from the prior art available. Even by artificially combining the disclosures of Nadkarni and Staniforth the person skilled in the art would not arrive at the currently claimed invention.

None of the Nadkarni or Staniforth formulations have a slower first phase of release when compared with the second phase of release. This is the inventive concept behind the currently claimed invention, Claim 34 of the current application recites,

> "a sustained release formulation of lamotrigine or a pharmaceutically acceptable derivative thereof in which there are two phases in the release of lamotrigine or a pharmaceutically acceptable derivative thereof, wherein the release rate in the first phase takes place in the oesophagus and stomach and is slower

than the release rate in the second phase which takes place when the surrounding pH exceeds 5...".

Neither Nadkarni nor Staniforth appreciates Applicants problem so therefore separate or together they cannot teach Applicants' solution. Neither Staniforth nor Nadkarni provides a system wherein the lamotrigine/active is released in two phases, the first phase having a slower release rate than the second. Nor does the combination of the teachings within Staniforth and Nadkarni achieve a slower first phase of release than the second because with the impermeable coating, there can never be a second phase of release faster than the first. Nor do they suggest a reason to do so. It is only when armed with knowledge of the present invention that a person skilled in the art would attempt to assemble the invention from the two prior art references.

Therefore the invention is non-obvious over Nadkarni in view of Staniforth.

It is believed that the application is in condition for allowance. Therefore, reconsideration and allowance is requested.

Applicants hereby request a face-to-face interview with the Examiner, should the Examiner not find the application as amended in condition for allowance. In order for the interview to take place, Applicants wish to advise the Examiner that interested parties for the interview will be attending from the United Kingdom and/or Canada so extra preparation may be involved to schedule and grant such an interview.

The Commissioner is hereby authorized to charge any fees required or credit any overpayment to Deposit Account No. 07-1392.

Respectfully submitted,

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